CERTIFICATE

This is to certify that this dissertation entitled **"DOES INTRAVESICAL GENTAMICIN INSTILLATION DURING RENAL TRANSPLANTION REDUCE POSTOPERATIVE URINARY TRACT INFECTION?"** is a bonafide work done by **Dr. Ajit J. Thomas** in partial fulfillment of the rules and regulation for M.Ch. Br. IV (Genitourinary Surgery) examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be held in August 2008.

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INTRODUCTION

Infectious diseases have been a constant yet evolving problem in the renal transplant recipients. The reduction in the incidence and severity of complications related to infection, can be attributed to multiple factors: improved surgical techniques, alterations and improvement in immunosuppressive regimens, institution of prophylactic antimicrobial agents, better diagnostic armamentarium, and the availability of more effective means of preventing and treating certain types of infection. This is reflected by the fact that during the first decades of the renal transplantation era, serious infectious complications developed in up to 70% of patients following transplant, resulting in fatal outcomes in as many as 11% to 40% of cases. (1, 8, 9, 11, 12, 13, 16) Recent studies have described an incidence of 15% to 44%, with mortality rate due to infections of less than 5% (2,3, 4,5, 6, 7, 10, 13, 14, 16 and 17).

Urinary tract infection continues to be the most common infection among renal transplant patients in Christian Medical College hospital. Infections continue to cause post-transplant morbidity and

remains a leading cause of death of renal allograft recipients at all points in the post-surgical course (8, 10, 13 and 15). The prevention and effective treatment of infectious complications remain major concerns of the transplant clinicians.

The high incidence of urinary tract infection (UTI) following renal transplant patients at our center has been of concern for the transplant team. A retrospective study of the first 30 transplants done in 2006 showed a 50% incidence of bacteriuria, hence a prospective study was planned to determine the incidence, predisposing factors if any, and ways to decrease them.

This study was initiated as a part of continuing efforts to improve the care of renal transplant recipients and to explore ways to decrease postoperative morbidity arising specifically out of infections in the urinary tract.

AIMS AND OBJECTIVES

The objective of this study was to evaluate specific strategies to reduce the incidence of bacteriuria after ascertaining the true burden of the problem in a prospective and controlled fashion.

The primary objective of this study was to prospectively determine in a randomized manner, whether gentamicin instillation into the urinary bladder at renal transplant, reduced the incidence of UTI during first 2 months following transplant and/or if there was a delay in the incidence of UTI in the same time period.

The secondary aim of the study was to evaluate whether a per-operative dose of antibiotic decreased the incidence of such infections in those with sterile urine prior to the transplant.

REVIEW OF LITERATURE

POST TRANSPLANT UTI: BURDEN OF THE PROBLEM.

Urinary Tract infection is the most common infection seen after kidney transplantation. The exact incidence remains a subject of debate with different studies reporting widely varying incidence rates (18,19,20). While the effects of early or late UTI after kidney transplantation on graft life and patient mortality has been controversial, some studies report adverse effects of UTI on both parameters (21). Other studies have failed to demonstrate a causal relationship though (21, 22). Risk factors for developing UTI after kidney transplantation have been numerous and varied. They have included female recipient gender, white or black race, deceased donor source of kidney, reflux kidney disease, and use of azathioprine or cyclosporin A (19, 23).

In a study involving analysis of the USRDS database for UTI in adult kidney transplant recipients; the cumulative incidence of early UTI was 17% for both genders (A). By 3 years after transplantation, the cumulative incidence was 60% in adult female recipients and 47% in adult male recipients. Recent articles from single centers have also reported similar frequencies. In a study of

adults, the occurrence of late UTI more than 6 months after transplantation was associated with a significantly higher risk for both graft loss and patient death. Factors that were associated with a higher risk for developing UTI after kidney transplantation in the adult population included female sex, black race, primary renal disease being chronic obstruction, chronic pyelonephritis, or polycystic kidney disease; recipient history of diabetes; and acute rejection episode in the first 6 months (24).

PHYSIOLOGY OF THE BLADDER

The uroepithelium lines the inner surface of the renal pelvis, the ureters, and the urinary bladder, where it forms a tight barrier that allows for retention of urine, while preventing the unregulated movement of ions, solutes, and toxic metabolites across the epithelial barrier. In the urinary bladder, this barrier must be maintained even as the organ undergoes cyclical changes in pressure as it fills and empties. Recent analysis of the uroepithelium has provided information on how detergent-insoluble membrane/protein domains called plaques are formed at the apical plasma membrane of the surface umbrella cells, how mechanical stimuli such as pressure alter exocytic and endocytic traffic in epithelial cells such as umbrella cells, and how changes in

pressure are communicated to the underlying nervous system.

Epithelial cells line the inner surfaces of organ systems and the urogenital tract is no exception. In the case of the urinary tract (including the renal pelvis, ureters, and bladder), the surface is coated by a specialized epithelium called the uroepithelium. The uroepithelium is stratified and is comprised of three cell types including basal cells, intermediate cells, and umbrella cells. Basal cells are small (10 _m in diameter), form a single layer that contacts the underlying connective tissue and capillary bed, and serve as precursors for the other cell layers. Their estimated half-life is 3–6 months. (25,26). Intermediate cells are pyriform in shape (10–25 am in diameter), sit above the underlying basal cells, and form a layer that appears in cross-section anywhere from one to several cell layers thick. The outermost umbrella cell layer is comprised of very large polyhedral cells with diameters of 25–250 am. Although umbrella cells are long lived, they are rapidly regenerated when the uroepithelium is damaged. This regeneration can result from cell division within any of the three cell layers, and generation of the multinucleate umbrella cells is likely due to intermediate cell–cell fusion (26).

A primary function of the uroepithelium is to form a barrier that

prevents entry of pathogens and selectively controls the passage of water, ions, solutes, and large macromolecules across the mucosal surface of the cell into the underlying tissue. Barrier function depends, in part, on the presence of specialized membrane domains that form a seal between the plasma membranes of adjacent epithelial cells. In the case of the uroepithelium, high resistance tight junctions are found in the umbrella cell layer that effectively divide the cell surface of these cells into apical and basolateral membrane domains (27). In addition, the apical membrane of umbrella cells has a unique lipid and protein composition that also contributes to the low permeability of this membrane domain to water and solutes (27-29)

The bladder epithelium was long treated as an impermeable cellular plastic coating that allowed for urine storage, and the majority of analyses of the lower urinary tract have focused on the bladder musculature and innervation. A renewed interest in the uroepithelium indicates that it can alter the ion and protein compositions of the urine as well as selectively allow transport of substances into the body via the bladder wall (27,30,31).

THE ROLE OF THE GAG LAYER

The GAG layer has been the controversial subject of urothelial barrier function. Parsons and associates (32) observed that after pretreatment with protamine sulfate there was an increase in rabbit urothelial permeability, both in vivo and in vitro, to water, urea, and calcium. This effect was reversed with pentosanpolysulfate (PPS). They concluded that the protamine sulfate affected the GAG layer, and that this was repaired by PPS. However no microscopic evidence of the anatomical changes were borne out in this paper. Nickel and colleagues, who performed the study (33) compared PPS and heparin and hyaluronic acid as treatment groups. The authors concluded that heparin was the best of the three agents in efficacy, but pointed out that this may be due to its anti-inflammatory properties. Others have suggested that the primary role of the GAG layer may be more in line with an antibacterial adherence function, as outlined by Hanno and associates. (34) The GAG layer may also be important for the formation and attachment of particulates to the urothelium and stone formation. (35,36)

However, there are several problems with the theory of the GAG layer being the primary urothelial plasma barrier. The first is that protamine sulfate can be used as a cytodestructive agent. (37)

Second, the GAG layer does not prevent small molecules such as amiloride from reaching, and subsequently interfering with, the sodium channels expressed on the surface of the umbrella cells. Third, the polyene antibiotic nystatin can reach the urothelium, as evidenced by increases in the short-circuit currents and reduction in transepithelial resistance to insignificant values as it generates nonspecific cation pores in the cholesterol-containing luminal membrane of the umbrella cells. Fourth, using microelectrodes, the first resistive barrier found is upon entry into the cell. Fifth, addition of monomeric arginine or polyvalent cations does not alter transepithelial ion permeability based on electrical measurements. Sixth, use of hydrolytic agents such as neurominidase, hyaluronidase, or chondroitonase, or a proteolytic agent such as trypsin or kallikrein (to deliberately strip the urothelium of the GAG layer) does not alter the ability of protamine to increase the urothelial permeability. (38) This implies that the protamine does not act at the level of the GAG layer but rather at the level of the luminal umbrella cells. Regardless, one cannot discount the possibility that under certain conditions the GAG layer may play a supportive role in barrier function. These data help infer the fact that the GAG layer probably has a prominent supportive role than as a primary barrier which may well be the role of the urothelium.

ROLE OF TRANSITIONAL EPITHELIUM IN DRUG TRANSPORT AND INFECTION

The apical surface of umbrella cells contains unique structural and biochemical features. Under an electron microscope the surface of the umbrella cells, appears undulating and a tight junctional ring surrounds each cell. Raised ridges, also called hinges or microplicae, and intervening areas called plaques, cover this surface. The arrangement of hinges and plaques give the apical surface its characteristic scalloped appearance, which is apparent when the apical surface of cross-sectioned umbrella cells is viewed by transmission electron microscopy. The hinge areas are not well understood, but contain at least one unique protein called urohingin (39), and presumably all other non-plaque proteins. Plaques are thought to occupy approximately 70–90% of the surface of the umbrella cell (26,40,41).

The membrane associated with the hinge and plaque regions is highly detergent insoluble, even in relatively harsh detergents like sarkosyl (42). The detergent insolubility may reflect the unusual lipid composition of this membrane, which is rich in cholesterol, phosphatidyl choline, phosphatidyl ethanolamine, and cerebroside – a lipid profile similar to myelin (43). Cholesterol-rich and

detergent-insoluble membranes form ‘rafts’ and cavalla (44). Essentially, the entire apical surface of the umbrella cell is composed of two lipid raft sub domains: plaques and hinges, which play a prime role in its insolubility.

The membrane associated with the plaque regions, have two layers (leaflets) and the outer leaflet appears to be twice as thick as the inner leaflet, thus forming an asymmetric unit membrane (AUM) (40,45,56). The AUM is composed of a Para crystalline array of 16-nm diameter AUM particles and exhibits six-fold symmetry. They are composed of an inner ring containing six large particles and an outer ring containing six small particles, and each subunit forms a twisted ribbon structure (46). A plaque is comprised of 1000 to 3000 AUM particles.

Potential constituents of the AUM particles include the uroplakins (UPs), a family of at least five proteins including the tetraspan family members UPIa and UPIb, and the type I single-span proteins UPII, UPIIIa, and UPIIIb (47,48). UPIa, UPII, UPIIIa, and UPIIIb are only expressed in the uroepithelium and are concentrated in the umbrella cell layer UPIa serves as a receptor for uropathogenic Escherichia coli (49,50, 51). How UPs combine to generate the six-fold symmetry of the AUM particles is

currently unknown. Furthermore, the currently described UPs may not be the sole constituents of AUM particles, as there are other proteins associated with plaques, such as antigen recognized by the AE-31 monoclonal antibody that have not been characterized (52).

ROLE OF TRANSITIONAL EPITHELIUM IN INFECTION

It is understandable from above that integrity of epithelium is essential also for prevention of infection. Normal urinary constituents do not therefore interfere with bladder permeability and changes within the physiological range for urine pH, calcium, or urea concentrations have minimal effects on the barrier function of the urothelium as determined from measurements of the transepithelial resistance (53). Nonphysiological concentrations of these substances, e.g., acid pH, low calcium, or high urea (4, 51), cause an increase in the ion permeability of the urothelium. The sites of increased ion permeability are at the apical membrane and tight junction. After pH, calcium, or urea return to normal values, the permeability of the urothelium returns to control values (26).

Similar situation ensues in cases of infection. A number of nonphysiological factors and bacteria alter the barrier function of

the urothelium. These include bacterial products such as amphotericin B, nystatin, gramicidin, polymyxin B, and perhaps alpha -hemolysin as well as positively charged proteins released from eosinophils and found in sperm (histones and protamine; (54). All of these substances increase the ion permeability of the urothelium by interacting with the apical membrane and causing a nonselective increase in membrane ion permeability. If the increase in membrane permeability persists, cell swelling and lysis will occur. The loss of cells from the epithelial layer results in a loss of barrier function.

RESPONSE OF BLADDER EPITHELIUM TO FILLING

The response of the uroepithelium to cyclical changes in hydrostatic pressure as the bladder fills and empties has been a subject of considerable research. In the bladder, pressure rises in a tri-physic manner as the organ fills with urine. The first rise occurs rapidly and then pressure remains relatively constant for an extended period of time called the storage phase. The storage phase is followed by the maturation phase, which is characterized by a rapid rise in bladder pressure, punctuated by large spikes in

pressure as the smooth muscle contracts. Upon voiding, the pressure returns to baseline and the process begins anew. A crucial aspect of the barrier function of the uroepithelium is that it must be maintained in the face of these changes in hydrostatic pressure.

The increased urine volume is accommodated by the uroepithelium in at least two ways. The chief mechanism is likely to be unfolding of the mucosal surface, which is highly wrinkled in the empty bladder. The other mechanism occurs at the cellular level and involves transitions in the morphology and function of the uroepithelium. As the bladder fills, the uroepithelium becomes thinner, apparently the result of intermediate and basal cells being pushed laterally to accommodate the increased urine volume (26). The umbrella cells undergo a large shape change that involves progression from a roughly cuboidal morphology in the empty bladder to one that is flat and squamous in the filled bladder (26).

MODELS OF SUBSTANCE TRANSPORT

In the classical model for vesical dynamics, the umbrella cell shape transformation is hypothesized to be accompanied by discoidal/ fusiform vesical exocytosis. This would increase the apical surface

area of the umbrella cell and the overall surface area of the bladder, allowing the bladder to accommodate additional urine volume (55,56). Upon voiding, it is hypothesized that apical membrane added during filling is rapidly internalized, replenishing the pool of discoidal vesicles. An alternative model proposes that there are no changes in umbrella cell surface area and, instead, changes in umbrella cell shape are accomplished by folding/unfolding of the apical plasma membrane (57).

EXOCYTOSIS AND ENDOCYTOSIS IN RESPONSE TO INCREASED HYDROSTATIC PRESSURE

It is widely believed that pressure induces exocytosis of discoidal/fusiform vesicles, resulting in increased umbrella cell apical surface area. Recent studies have demonstrated isolated tissue that increased hydrostatic pressure stimulates a 50% increase in apical surface area that is coupled with a significant decrease in vesicle surface area (55). This change occurs gradually (over a 5-h time period), indicating that exocytosis is a graded process.

Studies with specialized assays have demonstrated that increased hydrostatic pressure not only stimulates exocytosis, but also stimulates rapid endocytosis (55). The endocytosed membrane components including UPs are likely delivered to lysosomes,

where they are degraded (55), although this has not been formally proven. Whether recycling of internalized membrane is occurring is also unknown. Apparently, the rates of endocytosis and exocytosis are such that the net effect is to add membrane to the apical surface of the cell.

These data lead to a refinement of the classical model for vesicle transport to include an endocytic pathway that operates simultaneously with the exocytic pathway (55).

At first glance, the fact that hydrostatic pressure would simultaneously induce exocytosis and endocytosis seems illogical; however, hydrostatic pressure-induced endocytosis would modulate the increase in apical surface area brought about by exocytosis, and it would ensure turnover of membrane components such as AUM particles.

As described earlier, AUM particles may play important roles in barrier function and plasma membrane events. Furthermore, endocytosis and exocytosis are coupled in other cell types, such as neurons, where these two processes maintain the unique composition of the presynaptic membrane (59). Not much is known about the pathways for endocytosis (60) but umbrella cells may provide a model system to define the machinery that drives

them and study how they are regulated.

Recent evidence indicates that exposing the apical surface of the epithelium to hypertonic solutions stimulates apical endocytosis (61), but the mechanism is unknown, and endocytosis that accompanies return from hypotonic medium (which causes cell swelling) to isotonic medium is blocked in cells treated with the actin disrupting agent cytochalasin B (62), indicating a role for actin in umbrella cell apical endocytosis.

EVENTS FOLLOWING VOIDING

The classical model proposes that, upon voiding, apical membrane added during filling is rapidly endocytosed. Although highly likely, the current evidence is scant. However, filling the bladder increases hydrostatic pressure and induces the hydrostatic pressure-stimulated endocytosis described above (55). Other evidence comes from studies in which endocytosis was studied in tissue placed in hypotonic, then isotonic buffers (63); however, the physiological significance of this experimental manipulation is unclear. Finally, there is evidence that short-term application of hydrostatic pressure (for 5 min) across isolated uroepithelium increases surface area, and this increase returns to baseline when

the pressure is released, presumably the result of endocytosis (62). The intracellular fate of membrane internalized after voiding is an open question. The classical model proposes that it serves to reestablish the population of discoidal vesicles (64,58). However, there are few data that support this conclusion. In fact, endocytosed marker proteins (including fluid-phase and membrane-bound lectins) only label a small fraction of the total discoidal vesicle pool (65, 58, 66), indicating that the majority of discoidal vesicles may be formed de novo along the biosynthetic pathway.

SENSING BLADDER FULLNESS: CROSS-TALK BETWEEN THE UROEPITHELIUM AND THE NERVOUS SYSTEM

A growing body of evidence indicates that epithelia exposed to mechanical stimuli, such as those lining the gut, blood vessels, airways of the lung, and lower urinary tract, receive and transmit signals to submucosal neurons (67,68). In the case of the bladder, there is evidence that the uroepithelium may communicate bladder fullness to the underlying nervous system through a paracrine signaling pathway involving ATP release (67, 68).

SUMMARY AND PERSPECTIVES

The composition of urine is markedly different from plasma, with urine osmolality ranging from 50 to 1200 Osmol, a pH ranging between 4.5 and 10, and containing high concentrations of ammonia, urea, as well as other toxins. In humans, the bladder must store this urine for prolonged periods of time without permitting the passage of highly permeable molecules such as ammonia into the bloodstream. The barrier to ion, solute, and toxin flux is formed by the uroepithelium, which lines the inner surface of the bladder and must also adapt to large variations in pressure as the bladder fills and empties.

In addition, study of the uroepithelium is providing clues to how epithelial cells sense mechanical stimuli such as pressure, and transduce changes in these stimuli into cellular events such as membrane traffic. Increased pressure, for example, stimulates exocytosis and endocytosis in umbrella cells. There are other factors, which promote or prevent bacterial or chemical translocation across the urinary epithelium. Finally, the uroepithelium interfaces with an underlying nervous system, and bidirectional signaling between these two systems may communicate the degree of bladder filling, and may allow the nervous system to modulate uroepithelial barrier function.

Knowledge of these mechanisms is being used to fight urinary infections and promote bladder as a route of drug administration in a variety of pathogenic states.

BLADDER AS A ROUTE OF DRUG ADMINISTRATION.

Intravesical delivery of drugs have been used for treatment of Overactive bladder e.g. oxybutinin, and Transitional cell carcinoma e.g. Mitomycin With the possible exception of latter treatment of other pathological states via the bladder route have never really gained popularity as this method of delivery is just too cumbersome, as it requires repeated manipulation (bladder catheterization 3 to 4 times a day) of the lower urinary tract. Unless one is considering a patient already on clean intermittent self-catheterization, most patients will not accept this complex form of therapy.

In case of drugs like oxybutynin very high levels can be achieved with minimal systemic side effects. The reason lies in the fact that the majority of the effects on the salivary gland are produced by the oxybutynin metabolite desethyloxybutynin, which is produced not only by first-pass metabolism in the liver but also by direct

cytochrome P450 metabolism in the gut wall. (69) With oxybutynin XL, the drug is delivered at a steady rate for 24 hours, spending only 3 to 5 hours in the upper gut. (70) Therefore gut wall metabolism and first-pass metabolism in the liver are proportionally reduced, and subsequently one finds a reduced ratio of metabolite to parent compound systemically. This means one can achieve greater efficacy on the bladder with less dry mouth.

Antineoplastic agents like Mitomycin C usually have 1 time use and can be instilled at surgery and the scope of action mainly remains local hence is an attractive intravesical option.

For antibiotics too instillation can be an attractive form of brachytherapy that has distinct advantages. It avoids GI upset and alteration of gut flora can be avoided.

The principal concerns remained about effectiveness, bladder epithelial irritation, toxic absorption, and the inconvenience of having to pass a catheter. These perceptions are reflected in many of the early studies of instilled antibiotics that focused on individuals who were irrigated through indwelling catheters as a prophylactic measure against perioperative cystitis (72, 72, 73). Chamberlain and Needham investigated polymixin B, bacitracin and neomycin irrigations in women who underwent hysterectomy. Giannoni et al (73) evaluated 300 men who were irrigated with

povidone-iodine after transurethral resection of the prostate. These studies and others found fewer episodes of symptomatic bacteriuria while patients were on irrigation, but also confirmed suspicions about possible limitations of the technique. Certain agents such as acetic acid irritated the bladder epithelium and caused ulcers. (74) Others such as chlorhexidine were poorly effective against common iatrogenic pathogens such as Pseudomonas. (75)

If constant, therapeutic levels of drugs in the bladder can be achieved without repeated instrumentation, this would provide an extremely effective regimen to treat bladder pathologies. A similar situation can be envisaged in case of antimicrobials in UTI wherein significantly higher levels can be maintained in the bladder for long duration in susceptible individuals without risking toxicity of the drug in question.

AMINOGLYCOSIDES: THE PHARMACOLOGY, SPECTRUM AND INTRAVESICAL USE

The use of gentamicin sulfate intravesically is nothing new. Though the safety of the drug when used intravesically has never

been in doubt, its efficacy remains to be validated in large-scale studies. Literature availability so far has been limited to small studies and anecdotal reports.

Mc Guire et al (76) empirically used gentamicin sulfate for prophylaxis and treatment of bacterial cystitis for ten years in adult spinal-cord-injured patients on CIC who periodically experienced bacterial cystitis if not kept on oral antibiotics, and sometimes, in spite of medication. The infections were asymptomatic or presented with cloudy malodorous urine or new-onset urinary leakage. None were febrile, but all had bacteriuria and all had positive urine cultures. When Gentamicin instillation began, the urine cleared, cultures would become negative, and patients could stop taking oral agents. About 10 percent of all adult spinal-cord-injured patients evaluated by the authors, utilized intravesical gentamicin in this manner (84).

Gentamicin sulfate is an ideal intravesical antibiotic. It is a proven bactericide against most genitourinary pathogens (especially Pseudomonas species and other gram-negative organisms). First isolated as a derivative of Micromonospora purpurea in 1963, gentamicin has been widely used intravenously. (78) Commercially synthesized as gentamicin sulfate, it is highly cationic and does not easily cross lipid membranes. When

administered orally, it is poorly absorbed, although absorption has been noted when exposed to serosal surfaces, burns, and wounds during lavage or irrigation. (78) Findings by the same group of authors in the rat model suggest that severe inflammation does increase absorption from the bladder. The canine and human data suggest that high intravesical pressure and vesicoureteral reflux without inflammation do not they predispose to increased absorption. However, although significant levels of absorbed gentamicin did not develop in any patient, further studies are needed to determine if monitoring of serum gentamicin levels is necessary in patients with bladder augmentation, renal failure, or those taking immunosuppressive drugs. The effects of storage conditions are important to the usefulness of gentamicin sulfate as an intravesical agent. For outpatients the convenience and economy of being able to prepare liter quantities of irrigation solution and store at room temperature is appealing. It is known that GS is more potent in an alkaline environment. Increased acidity can increase the minimal concentration needed to inhibit the growth of gram-negative bacilli eight to thirtytwo-fold. (79) Prolonged exposure to higher temperatures (> 20 C), oxygen, and plastics has been identified as a factor that can lead to a loss of antimicrobial activity. (80,81). The in vitro data demonstrate that gentamicin sulfate can be safely stored without refrigeration or

alkalinization and remains potent for up to two months. Intravesical instillation of gentamicin sulfate is safe and effective. For patients who perform CIC it should be considered as a route of prophylaxis against recurrent simple bacterial cystitis. It obviates the need for oral agents and their attendant risks. This evaluation of gentamicin has established the criteria by which other potential intravesical antimicrobial agents can be judged: it has a low risk of absorption across a spectrum of clinical situations, it is highly effective against likely pathogens, and it demonstrates prolonged stability without special storage conditions.

MATERIALS AND METHODS

The authors sought to determine whether instillation of Gentamicin during bladder distention affected the incidence of urinary tract infections in the immediate post operative period following renal transplantation. The concept of antibiotic instillation, though not new has not been tried using gentamicin, especially in a setting of renal transplant patients. The fact that it is an urinary antimicrobial, effective against most pathogens and its systemic use being precluded in renal failure patients prompted its choice as the agent in this study. A randomized, double-blinded placebo controlled study was designed to see if aminoglycosides could prevent development of urinary tract infections in renal transplant patients in the immediate post operative period.

SAMPLE SIZE DETERMINATION AND STATISTICAL ANALYSIS

The sample size was calculated with the aid of a statistician.
Considering a 50% decrease in incidence of UTI as significant in the treatment arm and a power of 90% a figure of 170 was arrived at. Thus a total of 170 patients were to be randomized and placed in the

plain saline arm, or the saline plus Gentamicin arm. Block randomization with blocks of size varying between 4 to 8 were allocated to each group and sub stratification into the two units were made. The randomization was performed in the department of Biostatistics, using computer-generated numbers. This was sealed and delivered to the pharmacist who prepared the vials containing the Gentamicin or placebo and packed as mentioned above. The statistician and the pharmacist had no role in the actual conduct of the trial whatsoever. The principal investigator remained blinded in the study.

Statistical analysis was planned at the end of stipulated time or after 170 patients had gone through the procedure, whichever came earlier. Considering a p value of .05 the results was to be analyzed. A total of 44 patients were accrued at the end of the stipulated time period.

Clearance was obtained from the Institutional Review Board (IRB) and from the ethics committee, for the conduct of the study. As the department of Urology has two units with different antibiotic protocols the patients were sub stratified into two groups. The patients operated in unit 1 received 1 Gm of Augmentin and Ceftazidime each at surgery. Those operated in unit 2 did not receive any antibiotic. All were randomized into the placebo or antimicrobial group. The placebo used was normal saline. The

contents of commercially available Gentamicin were repackaged in glass vials in the institutional pharmacy and sterilized. These had a shelf life of six months. Gentamicin being a clear solution was indistinguishable from the normal saline, which was also packaged in similar glass vials with exactly similar labeling. The labeling differed only in the serial number of each vial, which ranged from 1 to 88, in two sets. These vials sere then placed into plastic bags of 5 each and each set assigned to one of the two cardboard boxes. Box 1 was used for Unit-1 transplants and the Box 2 for Unit-2 transplants.

The per-operative antibiotic protocols existing in both units were strictly adhered to, during the course of the study. All patients had a documented negative urine culture as laid down in the protocol.

Once the patient was anaesthetized the bladder was washed with 50 ml of normal saline and a 10 ml aliquot was collected in a sterile container and sent for culture. The bladder was then distended with saline or saline mixed with 240 mg of gentamicin unknown to the author who was present, personally instilling the solution.

The solution for instillation was constituted in the following manner: while the patient was being draped, 250 mls of I.V normal saline was placed a large kidney tray and the floor nurse, unaware

of the actual contents of the vial, broke the seal of the vial and poured its contents into the kidney tray after meticulously checking the serial number and the package of origin of the vial. The antibiotic protocol was uniformly adhered to in each group preoperatively. As is practiced, patients in Unit-1 received a single per-operative dose of 1 Gm Ampicillin and Sulbactam and 1 Gm Ceftazidime just prior to commencement of surgery. Patients in Unit- 2 received no antibiotic. The principal investigator and the patient were blinded to the study and were unaware as to who received the antimicrobial or placebo. The catheter was clamped and was released at the beginning of ureteroneocystostomy.

The Foley's catheter was removed once the urine output fell below 5000mls or on the following Monday (the day when patients are traditionally shifted back to the ward), whichever was later. The first culture sample was taken on the morning of the day one following catheter removal. This was a clean catch midstream sample, which was collected in the ward under supervision of the ward nurse. The cultures were repeated weekly for the next 12 weeks. The collection process was carried out under the supervision of the nurse or the doctor at around 12 noon on Wednesdays. This procedure was repeated every Wednesdays or when a UTI was suspected.

The patients were then followed up for 12 weeks. Culture positivity, febrile UTI, and other infections were documented.

RESULTS AND ANALYSIS

Table 1. Drug group and infection

Crosstab

			Infection		
			no	yes	Total
Drug group	placebo	Count	10	11	21
		% within Drug group	47.6%	52.4%	100.0%
	drug	Count	10	10	20
		% within Drug group	50.0%	50.0%	100.0%
Total		Count	20	21	41
		% within Drug group	48.8%	51.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.023[b]	1	.879		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	.023	1	.879		
Fisher's Exact Test				1.000	.563
Linear-by-Linear Association	.023	1	.880		
N of Valid Cases	41				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 9.76.

Table 2. Per operative antibiotic use * Infection

Crosstab

			Infection		Total
			no	yes	
Prior Antibiotic use	no	Count	9	9	18
		% within Prior Antibiotic use	50.0%	50.0%	100.0%
	yes	Count	11	12	23
		% within Prior Antibiotic use	47.8%	52.2%	100.0%
Total		Count	20	21	41
		% within Prior Antibiotic use	48.8%	51.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.019[b]	1	.890		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	.019	1	.890		
Fisher's Exact Test				1.000	.570
Linear-by-Linear Association	.019	1	.891		
N of Valid Cases	41				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 8.78.

Table 3. Drug group * Infection in the first week

Crosstab

			Infection in the first week		
			no	yes	Total
Drug group	placebo	Count	15	6	21
		% within Drug group	71.4%	28.6%	100.0%
	drug	Count	13	7	20
		% within Drug group	65.0%	35.0%	100.0%
Total		Count	28	13	41
		% within Drug group	68.3%	31.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.196[b]	1	.658		
Continuity Correction[a]	.011	1	.915		
Likelihood Ratio	.196	1	.658		
Fisher's Exact Test				.744	.457
Linear-by-Linear Association	.191	1	.662		
N of Valid Cases	41				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 6.34.

Table 4. Drug group * Infection in the second week

Crosstab

			Infection in the second week		
			no	yes	Total
Drug group	placebo	Count	15	6	21
		% within Drug group	71.4%	28.6%	100.0%
	drug	Count	15	5	20
		% within Drug group	75.0%	25.0%	100.0%
Total		Count	30	11	41
		% within Drug group	73.2%	26.8%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.067[b]	1	.796		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	.067	1	.796		
Fisher's Exact Test				1.000	.538
Linear-by-Linear Association	.065	1	.799		
N of Valid Cases	41				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.37.

Table 5. Drug group * Infection in the third week

Crosstab

			Infection in the third week		
			no	yes	Total
Drug group	placebo	Count	18	3	21
		% within Drug group	85.7%	14.3%	100.0%
	drug	Count	16	4	20
		% within Drug group	80.0%	20.0%	100.0%
Total		Count	34	7	41
		% within Drug group	82.9%	17.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.236[b]	1	.627		
Continuity Correction[a]	.005	1	.943		
Likelihood Ratio	.237	1	.627		
Fisher's Exact Test				.697	.471
Linear-by-Linear Association	.230	1	.631		
N of Valid Cases	41				

a. Computed only for a 2x2 table

b. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.41.

Table 6. Per-operative Antibiotic use * Infection in the first week

Crosstab

			Infection in the first week		
			no	yes	Total
Prior Antibiotic use	no	Count	13	5	18
		% within Prior Antibiotic use	72.2%	27.8%	100.0%
	yes	Count	15	8	23
		% within Prior Antibiotic use	65.2%	34.8%	100.0%
Total		Count	28	13	41
		% within Prior Antibiotic use	68.3%	31.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.229[b]	1	.632		
Continuity Correction[a]	.020	1	.888		
Likelihood Ratio	.230	1	.631		
Fisher's Exact Test				.742	.447
Linear-by-Linear Association	.223	1	.637		
N of Valid Cases	41				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.71.

Table 7. Per-operative Antibiotic use * Infection in the second week.

Crosstab

			Infection in the second week		
			no	yes	Total
Prior Antibiotic use	no	Count	15	3	18
		% within Prior Antibiotic use	83.3%	16.7%	100.0%
	yes	Count	15	8	23
		% within Prior Antibiotic use	65.2%	34.8%	100.0%
Total		Count	30	11	41
		% within Prior Antibiotic use	73.2%	26.8%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.688[b]	1	.194		
Continuity Correction[a]	.891	1	.345		
Likelihood Ratio	1.747	1	.186		
Fisher's Exact Test				.291	.173
Linear-by-Linear Association	1.647	1	.199		
N of Valid Cases	41				

a. Computed only for a 2x2 table

b. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.83.

Table 8. Per-operative Antibiotic use * Infection in the third week.

Crosstab

			Infection in the third week		
			no	yes	Total
Prior Antibiotic use	no	Count	15	3	18
		% within Prior Antibiotic use	83.3%	16.7%	100.0%
	yes	Count	19	4	23
		% within Prior Antibiotic use	82.6%	17.4%	100.0%
Total		Count	34	7	41
		% within Prior Antibiotic use	82.9%	17.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.004[b]	1	.951		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	.004	1	.951		
Fisher's Exact Test				1.000	.642
Linear-by-Linear Association	.004	1	.952		
N of Valid Cases	41				

a. Computed only for a 2x2 table

b. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.07.

Table 9. Native kidneys and infection

Poor Prognostic factors * Infection Crosstabulation

			Infection		Total
			no	yes	
Poor Prognostic factors	no	Count	19	15	34
		% within Poor Prognostic factors	55.9%	44.1%	100.0%
	yes (DM / FSGS)	Count	1	6	7
		% within Poor Prognostic factors	14.3%	85.7%	100.0%
Total		Count	20	21	41
		% within Poor Prognostic factors	48.8%	51.2%	100.0%

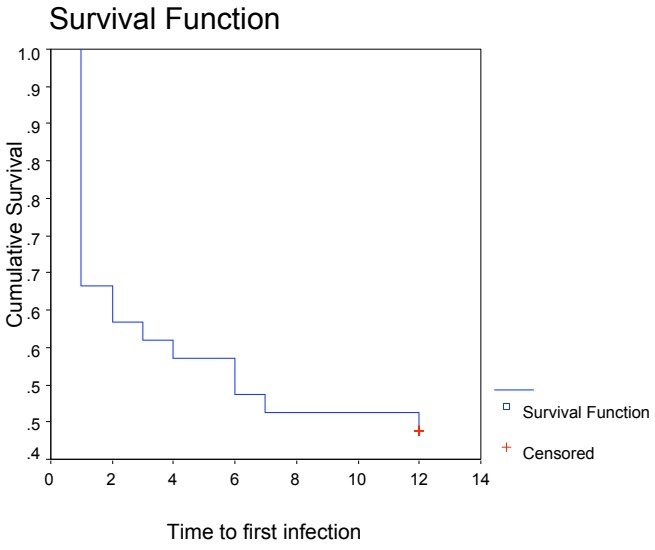
Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.020[b]	1	.045		
Continuity Correction[a]	2.528	1	.112		
Likelihood Ratio	4.410	1	.036		
Fisher's Exact Test				.093	.053
Linear-by-Linear Association	3.922	1	.048		
N of Valid Cases	41				

a. Computed only for a 2x2 table

b. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.41.

Table 10. Kaplan-Meier survival curve for time to infection



RESULTS

There were 23 patients in unit 1 and 21 from unit 2. The mean age of patients in unit 1 was 34.3 years with a range between 14 and 55 years. The mean age of recipients in Unit 2 was 35.7 years with a range between 20 to 61 years. There were 4 female recipients in unit 1 and 5 in unit 2. Therefore the demographics remained matched in both units in terms of age and gender. All patients received Tacrolimus based immunosuppression.

In all, there were 41 patients available for analysis. Two patients had graft nephrectomy in the first week and one patient died of non-septic complications in the second week. Eleven out of 21 patients had a positive urine culture that needed treatment in the first 3 months of transplant. In the 20 patients who underwent instillation 10 patients developed UTI. Nine (50%) of the 18 patients who did not have a per-operative of antibiotic at surgery developed UTI. This was similar to the Unit 1 group, which received a dose of antibiotic prior to surgery on the operating table. Twelve of the 23 patients from this unit developed urinary infection in the first 12 weeks.

Seven of the patients had either Diabetes or FSGS of who 6 contracted UTI. All four diabetics and 2 of the 3 FSGS patients

developed UTI.

A comparative analysis of the incidence of UTI at the end of first through third weeks in the gentamicin instillation group vs. placebo and the group that received per-operative dose of antibiotic versus those who did not, revealed no significant advantage for the intervention groups against the non-intervention groups. (Tables 3-8)

DISCUSSION

Aminoglycosides are effective antimicrobials in urinary tract infections but the fact that they are nephrotoxic precludes their use in renal failure patients especially via the parenteral route. Hence we analyzed if direct instillation of Gentamicin solution delayed the onset of UTI. Seven of the 20 who received Gentamicin instillation developed UTI at the end of first week whereas only 6 of the 21 who received placebo had the infection in the first week. However this did not achieve statistical significance (Tab 2). Neither did it delay the onset in subsequent weeks. Though not the primary objective we also looked at whether prior dose of antibiotic at surgery made a difference. The incidence of UTI in the Unit 1 group was no different from the Unit 2 group, which did not receive a dose of antibiotic on table, before surgery (table 1) the incidence of UTI in the subsequent weeks were also similar in both groups with neither Gentamicin instillation or prior antibiotic use making any difference.

Among the predisposing factors that may have affected the incidence of UTI, it was found that those with native disease of Diabetes Mellitus and FSGS had a higher incidence of UTI. This was statistically significant.

The time of onset of UTI was assessed in all patients across the

board. A Kaplan-Meier curve was drawn to analyze the time to infection. Interestingly majority of patients, who developed UTI, developed it in the first 6 weeks. Of these, more than 30% developed the infection at the end of the first week. This study showed that in any patient who did not develop UTI in the first 6 weeks, the chances of him/her developing the infection subsequently was negligible. This was in concordance with observations by Rubin (82). He categorized infections as those occurring within 1 month, 2-6 months, and thereafter. The first group included urinary infections, vascular access, catheter, and surgery related infections. A timetable for infections in renal transplant recipients, was published earlier from our institution, further validates these observations (83).

THE SPECTRUM

E coli was the most common organism. Klebsiella and pseudomonas was the next most common in two patients each. Enterococcus was found in one patient and was a mixed infection, combined with E coli. One patient had a mixed klebsiella-pseudomonas infection in the first week. Overall 13 (33%) patients were found to have bacteriuria following the first week of renal transplant.

Weeks	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
E coli	12	10	4	5	5	4
Klebsiella	1	2	1	0	1	1
Pseudo	1	2	0	1	1	1
Enterobact	1	0	0	0	0	0

Table 1: Spectrum of infections. The figures in boxes show no. of patients.

Under standard immunosuppression, a median of about 50% (range 6-86%) of all renal transplant recipients develop an infection within the first 6 months after engraftment. It is known that urinary tract infections are most common, with an incidence upto greater than 30% and a relatively high rate of bacteremia and overt pyelonephritis of the allograft (84). Infections in renal transplant recipients are therefore of major clinical as well as economical importance, and are one of the dominating causes of transplant loss and patient death. In a mortality study by West et al, (85) infections accounted for 22% of all deaths among renal transplant patients; this was even higher than myocardial

infarction, which caused 17%.

Urinary tract infections following transplant may be the result of indwelling catheter and or anatomic obstructions caused due to the surgery, particularly ureteroneocystostomy (84). Parenteral antimicrobial prophylaxis of the urinary infection associated with urethral catheterization in the post renal transplant period has been employed many transplant centers. There is a world trend towards the reduction of the use of this prophylaxis. When used, it needs to be initiated immediately before the surgery and if continued should not be used for more than 24 hours after the transplant (85) Systemic antimicrobial prophylaxis has not been demonstrated to be of value for the prevention of this infection. Besides, immunosuppression does not damage the natural defenses of the host when it is used over a few days in the renal post-transplant period and the immune system plays no part either in the bladder colonization or in asymptomatic bacteriuria (86). The asymptomatic bacteriuria is by far the most frequent infection after renal transplantation and can cause considerable morbidity when it is associated with urological, surgical or serious immune complications (87). Therefore this study was a part of yet another attempt to look for intervention to reduce such morbidity.

The number of days patients remain on indwelling catheter post

transplant is not standardized. There is a trend towards early removal of catheter with most centers stopping continuous bladder drainage by the fourth day (88). In this study the median period of catheterization was about 5 days, which is longer than mentioned in the literature. This probably explains why this study had a higher incidence of urinary infections in the first few weeks following transplant. This longer period of urethral catheterization may cause greater harm to the normal urethral flora and may lead to a higher incidence of urinary infection (85,89).

CONCLUSIONS

Gentamicin instillation into the bladder at a dose of 240 mgs during transplant surgery did not appear to provide any protection from urinary tract infections post operatively at any point in time.

Per operative dose of Augmentin and Ceftazidime also did not make any impact on the incidence of postoperative urinary tract infections.

Diabetics and those with focal segmental glomerulosclerosis appear to be at a greater risk of developing post transplant urinary tract infections.

However studies with a larger sample size are required to draw any statistically significant conclusions.

LIMITATIONS

This study had a major limitation in that patient accruals were inadequate. The number of patients enrolled fell short of the minimum sample size required. Hence it is possible that the interventions studied may have achieved statistical significance in a larger group of patients.

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Patient Name	Hospi	Seria	Uni	Wt	Date Sx	pre	On	post c/s	antibiot	Imm	Indu	NKD	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk6Z	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12	Colla
Anand Nayak	6471	5S	Z		4/19/2007	No	NG			I,M,	none	CAN	Pseu/Kl	pseu	NG	conta	NG	NG	NG	NG	pseud	pseu	Klebs	NG	NG	
Tapan Banik	2782	18S	Z	46	11/13/2007	neg	NG			I,M,	ATG	CIN	NG	NG	NG	NG	NG	NG	NG	EC						ATI
Helal Ahmed	9644	10	I	52.5	5/15/2007	contam	NG		augme	I,M,	none	clmu	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Dasho Tsetrim	9066	Z	I		3/27/2007	contam	NG		augme	I,M,	none	DIM	NG		contamin	contami	contamin	11,000	EC	NG	NG	NG	NG	NG	NG	NO
Somnath M	9967	13S	Z	43	/14/2007	no	NG			I,M,	ATG	DIM	E coli	E coli	EColi	E coli	NG	NG	NG	E coli	E-coli	Klebsi	Klebsiella	Klebsiell	Klebsie	
Pattabhi Reddy	6415	15S	Z		9/19/2007	neg	NG			I,M,	ATG	DIM	NG	NG	NG											
Shrikant Pd	9854	16	I		10/9/2007	neg	NG		augme	I,M,	IL-2	DIM	EC	EC	EC	EC	EC	EC	EC	EC	EC	EC	EC	EC	EC	Post
Jaman Gurung	6846	21	I	51.8	11/8/2007	neg	NG		augme	I,M,	none	DIM	NG	EC, PA	cont	Pseud	cont	Pseud	Pseu	pseud	pseud					Febri
Laboni Pati	9376	13	I	41	8/20/2007	no	NG		augme	I,M,	IL-2	tsgs	E coli	E coli	NG 7/11	cont	cont	NG	NG	E-coli						Febri
Bhisma Raj	0034	14	I	55	7/17/2007	contam	NG		augme	I,A,	none	PSG	NG													
Raj Kumar	0312	16S	Z		10/3/2007	neg	NG			I,M,	none	PSG	NG	NG	NG	########	#######	EAP								
Saloni Ao	0866	19S	Z	43	11/14/2007	neg	NG			IMP	IL-2	PSG	NG	NG	NG	E Coli					E coli	E coli				
Dipa Dutta	9641	8S	Z	34	5/25/2007	contam	NG			I,A,	none	hype	E coli	E coli,	NG 8/14	NG 8/21	E coli	E coli	E coli	E coli	E coli	E coli	E coli	E coli	E coli	Had
Nanda Kishore	3297	6	I		4/11/2007	no	NG		augme	I,M,	none	MPG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Hemant Singh	9546	1	I			No	NG	No	augme	I,M,	none	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Kavita Kumari	3512	3	I		3/28/2007	contam	NG		augme	I,A,	none	UK	Entero,	E.coli,	E.coli,	NG	E.coli,	E.coli,	E.coli,	NG	NG	NG	NG	NG	NG	UTI,
Tshering W	9883	1S	Z	39.5	3/29/2007	staph	NG		augme	I,M,	IL-2	UK	E.coli,	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	one
Fazlul Sumon	8743	4	I	69.2	4/3/2007	cont	NG		augme	I,M,	none	UK	E.coli,	E coli	E coli	E coli	E coli				E coli	E coli	E coli			Persi
Chewang	3430	2S	Z		4/4/2007	no	NG			I,M,	none	UK	NG	NG	Kleb	NG	NG	NG	NG	NG	NG	NG	Candida A	NG	NG	Proto
Mau	7606	3S	Z		4/5/2007	no	NG			I,M,	none	UK	NG	NG	NG	NG	NG	Klebs	Cont	Cont	Cont	Cont	Cont	Cont	Cont	
Sonrab Ali	9787	5	I	63.6	4/10/2007	no	NG		augme	I,M,	none	UK	NG	NG	NG	NG	NG	NG	NG	NG	Cont	NG	NG	NG	NG	
Wangdup	8261	4S	Z	53.4	4/12/2007	no	NG			I,M,	none	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Subramani	9943	7	I		4/17/2007	no	NG		augme	I,M,	none	UK	NG	NG	Cont,	NG	NG	NG	NG	NG	MOA	MOA	NG	NG	NG	
Kishore Gurung	9314	8	I	50.2	4/24/2007	contam	NG		augme	I,M,	none	UK	E-coli	NG	E-coli	NG	NG	NG	E coli	NG	NG	NG	NG	NG	NG	
Kaushik Roy	9854	9	I	53	5/1/2007	no	NG		augme	I,M,	none	UK	NG	E-coli,	cont	Cont	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Habibdin	7893	7S	Z		5/16/2007	no	NG			I,M,	none	UK	NG	Cont	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Chandrakanta	9934	11	I	50.4	5/23/2007	no	NG		augme	I,M,	IL-2	UK	E coli,	E coli	cont	cont	cont	cont	cont	cont	cont	cont	cont	cont	cont	UTI
VANLALRUTLU	0055	12	I	51	6/5/2007	no	NG		augme	I,M,	IL-2	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Mond Abdur	4181	9S	Z	53	6/13/2007	no	NG			I,M,	IL-2	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Tarun Kumar	8902	10S	Z		6/14/2007	no	NG			I,M,	IL-2	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Dhan Bahadur	0292	11S	Z	59	6/27/2007	contam	NG	sepsis,		I,M,	IL-2	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Goshta Gopal	0223	12S	Z	57	6/26/2007	no	NG	fever,		I,M,	none	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Masud Rana	9808	14S	Z		7/16/2007	no	NG			I,M,	none	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Shikha	8580	15	I	14	7/31/2007	contam	NG		augme	I,M,	none	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	
Amarendra	0040	16	I	15	8/23/2007	no	NG		augme	I,A,	none	UK	EC,	EC	EC 9/17	EC 9/29	cont	EC	cont	NG	NG	NG	cont	NG	NG	NO
Taiphaba L	0324	17	I	56	9/18/2007	no	NG		augme	I,M,	none	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	Klebsie	Keje
Manas Kundu	0025	19	I		11/6/2007	neg	NG		augme	I,M,	none	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NC	
Tshering Dorji	0753	20	I		11/7/2007	neg	NG		augme	I,M,	IL-2	UK	EC	EC 11/19	NG 11/26	NG 12/5	NG 12/12	EC 12/6	EC	EC	EC	NG	NG	NG	NG	Febri
John Moses	0470	22	I	45.6	11/27/2007	neg	NG		augme	IAP	IL-2	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG					Post
Md Zahane	1370	23	I	62.9	12/18/2007	cont	NG		augme	IMP	IL-2	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG					
Amire Sultana	1346	21S	Z	39.4	12/20/2007	cont	NG			IMP	IL-2	UK	NG	NG	NG	NG	NG	NG	NG	NG	NG					
Humayun Kabir	9922	17S	Z		10/31/2007	neg	NG			I,M,	IL-2	UK ,	NG	0 0	0	0	0	0	0	0	0	0	0	0	0	
Jitendra	9871	9S	Z		5/10/2007	contam	NG			I,M,	IL-2	YUK	E.coli	NG	E-coli	E-coli	cont	cont	cont	E coli	E coli,	cont	cont	NG	NG	Frequ
Md Firoz Alam	1155	20S	Z	60	11/28/2007	neg	NG			IMP	IL-2		NG													

Informed consent for patients in the Gentamicin instillation study

Introduction

Hello, I am Dr Ajit J Thomas working in the Department of urology, CMC, Vellore. We are conducting a study, which we hope, will help us to lower the incidence of urinary tract infection following renal transplant. Currently post op urinary infections cause significant morbidity to the renal transplant patient, even causing the graft dysfunction. We believe instillation of dilute Gentamicin in urinary bladder might lower the post op incidence of urinary infections.

The study is entitled "Does intravesical instillation of Gentamicin during renal transplantation lower the incidence of postoperative urinary infections?"

Study procedure

If you participate, we will collect your medical history and check for your eligibility based on the records. If eligible you will be randomized into either of 2 groups. One group will have plain normal saline instilled at surgery and the other group will have 240 mg of gentamicin mixed to the normal saline before its instillation into the bladder. The fluid will remain in the bladder till the catheter is unclamped at he end of the ureteric implant.

Benefits

A possible reduction in the incidence of urinary infections is anticipated.

Risks

The risks are minimal, as it does not involve injection into your body. Most studies done on animals and humans do not show appreciate amounts of absorption into the body.

Compensation

You will not be entitled to any compensation for participating in the
Study

Confidentiality

Your name will not appear on the study record. Information regarding you will be kept a secret and only accessed for results and analysis of data.

Participation

Your participation is voluntary. You may withdraw from the study at any point in time before surgery. This will not affect your future treatment in the hospital. The investigator may also withdraw you from the study without your consent.

Reporting your experience

If you have had any bad experience, which you think may have been due to the drug, kindly feel free to contact Dr Ajit J Thomas at this no. 9944166911

I would like to know if you have understood my explanations and if you have any queries before participating in the study. If you agree to take part kindly sign or place your thumb impression on this document below.

Participants' statement

It has been informed to me in the language that I understand that this is a study being conducted to see if instilling Gentamicin into my bladder will alter the incidence of postoperative urinary tract infection.

I am aware that the study involves my randomization to either of the two groups depending on numbers generated by the computer. I'm aware that at the time of undergoing the surgery for renal transplant, I may or may not have diluted Gentamicin instilled in my bladder for a period of surgery; depending on which group I'm allocated to. The fluid containing gentamicin shall be removed at the end of surgery.

I am aware of the side effects of this drug when administered by injection. I have been assured that it does not involve injection of the drug into my body and there is only negligible amount of absorption of the drug when instilled as a dilute solution (240mg in 300 Normal saline) in the bladder.

I have read the consent document and have discussed with Dr Ajit J Thomas, the procedure described in the information sheet. I have had the opportunity to ask questions which have been answered to my satisfaction. I understand that any questions I may have asked will be answered verbally or if I prefer with a written statement.

I am aware that the participation is purely voluntary and does not involve any compensation. I may withdraw from the study at any time without assigning any reason, and this will have no bearing on the treatment in future in this institution.

I understand that any illness arising out of the consequence of Gentamicin instillation will be treated free of cost but I shall bear all other expenses.

If I have any questions regarding my rights , I may contact IRB in CMC, Vellore.

I am fully informed about the risks and benefits and hereby consent to the procedures set forth above.

I understand that my identity as a participant in the study, and my medical records and data will be kept confidential, except as required by law and for inspection by the study supervisors.

Date Signature of participant

I have fully explained to, the nature of the study and its attendant risks and benefits. I have answered all the questions to the best of my ability and knowledge.

Signature of investigator Signature of witness